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Removing the Bone Brake

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Osteoporosis results from an imbalance between bone resorption and bone formation. While bone resorption inhibitors are widely used to treat osteoporosis, stimulating bone formation is more challenging. Recently, McClung et al. (2014) found that neutralization of sclerostin, a potent inhibitor of bone formation, effectively increased bone mass in postmenopausal women.

Osteocytes, the most abundant cell type in the mammalian bone, are considered to have essential homeostatic functions. While entirely surrounded by mineralized tissue, these cells are interconnected by a dense network of bone channels. Osteocytes are the major source of receptor activator of NF-kB ligand (RANKL), an essential cytokine responsible for osteoclast activation and bone resorption, and specifically produce large amounts of sclerostin, one of the most potent inhibitors of bone formation in the body, making it an interesting target for treatment of bone disease in humans. As a key step in treating low bone density clinically while avoiding the side effects of RANKL inhibition, a recently conducted phase 2 trial showed that neutralization of sclerostin with a humanized monoclonal antibody (romosuzumab) significantly improved bone mineral density in osteoporotic women (McClung et al., 2014).

Sclerostin is the product of the SOST gene, which was found by geneticists in 2001 to be mutated in a few descendants of Dutch settlers in South Africa with excessively high bone mass (sclerostosis) (Balemans et al., 2001). Altered regulation of SOST was also found in a very similar syndrome of high bone mass, termed van Buchem disease, which was virtually exclusively confined to a few patients stemming from a small village in the Netherlands (Staehling-Hampton et al., 2002). The protein product of SOST, sclerostin, effectively controls bone formation by binding to the low-density lipoprotein receptor 6 (LRP6). Wnt proteins, which are powerful inducers of bone formation, bind to LRP6, thereby fostering the differentiation of mesenchymal precursor cells into bone-forming osteoblasts. Sclerostin interferes with this interaction and therefore effectively blunts bone formation (van Bezooijen et al., 2004). Although the uncontrolled bone apposition in the rare genetic absence of sclerostin supports its homeostatic function in the skeleton, dampening of sclerostin may have a therapeutic value in conditions of enhanced bone loss, such as postmenopausal osteoporosis, tumor metastasis, and inflammation-induced bone loss. In particular, its virtually exclusive expression in the bone tissue makes sclerostin an appealing therapeutic target.

That inhibition of sclerostin by neutralizing antibodies increases bone mass was initially shown in ovariectomized rats as well as in cynomologous monkeys. The first evidence that pharmacologic inhibition of sclerostin affects human bone came from a phase 1 study with the anti-sclerostin antibody romosuzumab (Padhi et al., 2011). A single dose of this antibody increased bone formation but decreased bone resorption markers. The recently published phase 2 trial by McClung et al. (2014) was larger, enrolling 419 postmenopausal women with low bone mineral density (T scores between −2 and −3.5), and defined changes of bone mineral density in the lumbar spine after 12 months as its primary endpoint. Dependent on the dose of romosuzumab (70, 140, or 210 mg monthly; 140 or 210 mg every 3 months), bone mineral density significantly increased between 5.4% and 11.3% in the lumbar spine compared to placebo treatment. Furthermore, two additional nonblinded treatment arms, with the bisphosphonate alendronate and the parathyroid hormone teriparatide, revealed that the lower dosing regimens of the anti-sclerostin antibody had comparable effects to alendronate and teriparatide on bone mineral density. Only higher doses, 140 mg and 210 mg of romosuzumab per month, increased bone mineral density beyond what was observed with bisphosophoates and teriparatide.

These findings provide solid evidence that inhibition of sclerostin is effective in increasing bone mass in osteopenic postmenopausal women. Analysis of markers of bone metabolism revealed a very rapid, but also transient, increase of bone formation markers. Hence, sclerostin could resemble a natural brake for bone formation, which, once neutralized, allows rapid differentiation of mesenchymal cells into functional osteoblasts (Figure 1). On the other hand, this anabolic effect on bone appears to fade over time, which may suggest that other natural brake mechanisms inhibiting Wnt-mediated bone formation, such as dickkopf-1, may step in for sclerostin (Diarra et al., 2007). Still, romosuzumab permits increasing bone mass, which may be additionally supported by decreasing bone resorption markers. The remarkable decrease of bone resorption after sclerostin inhibition may be explained by the induction of osteprotegerin, a natural inhibitor of RANKL, by the Wnt proteins (Diarra et al., 2007) (Figure 1). Inhibition of sclerostin would unchain Wnt signaling, thereby increasing osteprotegerin and suppressing RANKL-induced bone resorption (Figure 1). The divergent effects on bone formation and bone resorption after sclerostin inhibition are interesting, since some inhibitors, such as bisphosphonates and denosumab, suppress both processes, whereas parathyroid hormone increases both bone formation and bone resorption. Nonetheless, direct comparisons between bisphopshonates, teriparatide,

and romosuzumab on bone biomarkers must be considered with caution, since no blinding for these therapies was performed in this study.

Although the data from this phase 2 study are interesting, several questions remain. For instance, it is unclear whether the transient changes in markers of bone metabolism will translate into a long-term effect on bone mass and fragility. Furthermore, the long-term safety of sclerostin inhibition remains to be determined. Although even the excessive new bone formation observed in genetic absence of sclerostin is not associated with increased tumor burden, this point remains to be determined during pharmacologic blockade of sclerostin. It is also not yet known whether sclerostin inhibition may worsen joint fusion (ankylosis) in the context of pathologic new bone formation during inflammatory or degenerative joint diseases (Heiland et al., 2012). This issue appears to be important, since aged individuals are the primary target population of such treatment. Finally, since factors that influence bone resorption (RANKL) (Kiechl et al., 2013) and bone formation (osteocalcin) (Lee et al., 2007) control hepatic insulin resistance, and sclerostin levels are elevated in type 2 diabetes mellitus (García-Martín et al., 2012), the potential effects of sclerostin inhibition on insulin resistance and metabolism would have to be defined.

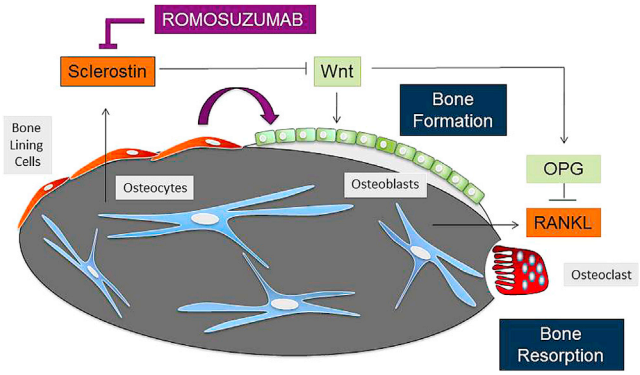

Figure 1. Effect of the Anti-Sclerostin Antibody Romosuzumab on the Bone

Osteocytes (blue) are embedded in the bone matrix (gray) and produce sclerostin as well as RANKL (orange). Sclerostin inhibits differentiation of bone-lining cells (red) into osteoblasts (green). Romosuzumab blocks sclerostin and removes the brake on Wnt protein-dependent osteoblast differentiation (arrow). Wnt proteins also stimulate the expression of osteoprotegerin (OPG), an inhibitor of RANKL, thereby blocking osteoclast-mediated bone resorption.

In summary, romosuzumab, a neutralizing antibody against sclerostin, will deepen our knowledge of the physiological role of sclerostin in the human skeleton and will additionally open new possibilities to fight bone loss in humans, which is a major challenge in the aging population.

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